4 Guidelines on Formulating Uncompressed Solids

I. RELATIVE HUMIDITY

Relative humidity in the filling and storage areas is more important for powders than for other dosage forms because of the large specific surface area (area/weight), which can result in significant moisture uptake. The gelatin capsule shells are also susceptible to moisture and degradation at high moisture. In addition, at very low moisture, gelatin in capsules can become very brittle; therefore, an appropriate humidity level must be maintained.

II. SURFACE AREA

The large surface area of powders provides greater opportunity for the production of static electricity during the friction of flow and handling. Make sure all equipment is well grounded or else significant segregation and impeded flow of powder can result. Monodisperse systems of particles of regular shape, such as perfect cubes or spheres, can be described completely by a single parameter; however, when either nonuniform size distribution or anisometric shapes exist, any single parameter is incapable of totally defining the powder. In addition to a value for the average particle size, often we use frequency histograms to help describe the powder. We also use other measures of powder characteristics such as angle of repose and bulk or tap density. Lastly, we use compressibility and the powder's ability to undergo plastic deformation.

III. SIEVE ANALYSIS

Dry sieving allows the fractionation of relatively coarse powders and granules. Sieves are stacked (*nested*) with the largest apertures at the top and the smallest at the bottom. A sample of powder is placed on the top sieve and shaken for a fixed time period at a given amplitude and pulse frequency.

The weight of powder on each sieve can then be calculated and the particle size distribution obtained. Particles must have a two-dimensional profile smaller than the sieve aperture in order to pass through a particular sieve. A *mean sieved diameter* is calculated. Because the weight of particles on each sieve is determined, the mean sieved diameter represents a *mass distribution.*

A mesh number denotes the size of the apertures in each sieve. The mesh number is the number of wire strands (of constant diameter) per inch used to weave the square mesh pattern. The side length of the aperture in microns is inversely related to the mesh number.

Whereas the specifications of starting materials are specified, the powders often form aggregates during storage; a point of use check of aggregation is needed. It is a good idea to sift all ingredients through specified sieves prior to adding them to mixing of blending vessels. For most raw materials, sifting through a No. 60 sieve (250 μm) is desirable; however, passing materials through finer sieves can generate electrostatic charges. Wet mass is passed through a No. 8 (2.38 mm) sieve and dried granules are passed through a No. 16 (1.19 mm) mesh sieve. Lubricants should be sieved through No. 60 mesh, except for magnesium stearate, which should not be shifted through an opening smaller than the opening in a No. 35 mesh. This is necessary to avoid building up electrical charges. A conversion chart for sieve sizes from U.S. Mesh to inches and microns (or millimeters) is presented next.

U.S. Mesh	Inches	Microns	Millimeters
3	0.2650	6730	6.730
4	0.1870	4760	4.760
5	0.1570	4000	4.000
6	0.1320	3360	3.360
7	0.1110	2830	2.830
8	0.0937	2380	2.380
10	0.0787	2000	2.000
12	0.0661	1680	1.680
14	0.0555	1410	1.410
16	0.0469	1190	1.190
18	0.0394	1000	1.000
20	0.0331	841	0.841
25	0.0280	707	0.707
30	0.0232	595	0.595
35	0.0197	500	0.500
40	0.0165	400	0.400
45	0.0138	354	0.354
50	0.0117	297	0.297
60	0.0098	250	0.250
70	0.0083	210	0.210
80	0.0070	177	0.177
100	0.0059	149	0.149
120	0.0049	125	0.125
140	0.0041	105	0.105
170	0.0035	88	0.088
200	0.0029	74	0.074
230	0.0024	63	0.063
270	0.0021	53	0.053
325	0.0017	44	0.044
400	0.0015	37	0.037

IV. PARTICLE SIZE DISTRIBUTION

Sieving is a common method for establishing the distribution of particle size in a powder sample. It is a simple method that works well for powders in the size ranges used most often in the pharmaceutical industry. Sieves are limited in that they cannot be made with very small openings. The current lower limit is 43 μm, which corresponds to a No. 325 sieve. The sieve number or mesh number refers to the number of openings per linear inch. You can easily calculate the opening size in millimeters. For example, a No. 2 sieve has an opening of 9.52 mm, while a No. 200 sieve has an opening of 0.074 mm.

A frequency histogram is a useful tool in understanding the nature of a sample of powder. It is a bar graph with the size range on the x-axis and the number or weight of each segment of the powder on the y-axis. The particle size distribution can be determined by a sample of coarse powder using a nest of sieves shaken in a sonic sifter:

1. Using at least a three-decimal-place electronic balance, record the weight of each empty sieve and the collection pan. Also record the sieve size.
2. Arrange the sieves in a sequential nest: smallest mesh number (largest aperture) at the top, largest mesh number (smallest aperture) at the bottom. Add the collection pan to the bottom of the nest.
3. Add approximately 5 g of accurately weighed coarse powder to the top sieve, and cover with the rubber cap.
4. Shake the sample for 5 min with a sieve "amplitude" greater than 3.
5. Reweigh each sieve and the collection pan. Calculate the weight and percentage of powder on each sieve and in the collection pan. Then calculate the cumulative weight percentage of powder that is finer than the aperture.
6. Use the probability paper to calculate the mean diameter and standard deviation; alternately, calculate the geometric mean and standard deviation for the coarse and fine powder particles.

V. POWDER FLOW PROPERTIES

During many pharmaceutical production processes, it is necessary to transfer large quantities of powder from one location to another in a controlled manner, for example, in powder blending, powder filling into containers (e.g., dusting powders), powder flow into capsules, and powder filling into the dies of a tablet press.

One method of assessing flow properties is the *Angle of repose*, which is another measure of the nature of the powder. It estimates the adhesive force between the particles. Uniform glass beads, which will show good flow properties, have an angle of repose of 23°. As the adhesive force between the particles increases, the angle increases. In rare cases, it can exceed 90°.

Powder is allowed to flow freely through a funnel onto the center of an upturned petri dish of known radius. When the powder reaches the side of the petri dish, the height of the cylindrical cone is determined. From the petri dish radius (r, cm) and cone height (h, cm), the angle of repose (between the petri dish and base of the powder cone) can be calculated. *Flow rate* can also be determined by measuring how fast a powder flows through an aperture. Free-flowing powders exhibit a high flow rate and a smaller angle of repose. Angle of repose and flow rate depend on particle size, shape, and surface roughness. Flow properties are frequently enhanced by the use of *glidants.*

Several commercial instruments are available to evaluate angle of repose. Follow the instructions from the supplier of instrument and test methods. A simple method is given here:

1. Measure the external diameter of a petri dish; position the bottom of a funnel or paper cone about 5 to 15 cm above the center of the upturned petri dish using a ring stand. Be sure a piece of paper is under the petri dish so you can pick up the powder and reuse the powder for all your replicates.
2. Slowly pour the *coarse powder* sample into the funnel, tapping the funnel as necessary to ensure that powder flows through the hole.
3. Continue this process until the bottom of the powder pile just begins to fall over the edge of the petri dish.
4. Measure the height of the pile using a ruler.
5. If the powder is lumpy, sieve it before beginning the experiment.
6. Repeat Step 2 until you consistently obtain the same answer.
7. Calculate the mean height of the coarse powder pile and the mean angle of repose (ϕ).

Note: Remember that Tan ϕ = Opposite/Adjacent, therefore, Tan ϕ = 2 h/D.

8. Repeat Steps 2 and 3 using both *fine powder* and *fine powder with glidant,* if the purpose is to select an appropriate glidant.
9. Plot angle of repose (x-axis) against Carr's index (y-axis).

VI. REAL, TAPPED, AND BULK DENSITY

Bulk or *tapped density* is a measure of the degree of packing or, conversely, the amount of space between the particles in the powder. Bulk density is determined by placing a sample of powder of known weight in a graduated cylinder. Tap density is determined by tapping the powder in the graduate until it no longer settles.

Many methods are also used to determine the true density of the powder (e.g., helium pycnometer or gas adsorption). Dividing the true density by the bulk or tap density yields a number that is related to the amount of space in the powder. If the particles are a sphere, the value is about 0.53, while irregular shaped particles can have values of 0.74 or more.

The *real density* of a powder sample is the weight per unit volume of the material with no air spaces between particles. Therefore, if a material has a true density of 1 g/cm^3, 100 g of material will occupy 100 ml, assuming individual particles fit together exactly. In practice, most powders do not fit together very well. Therefore, if one fills a graduated cylinder to 100 ml with a powder, the weight of powder required may only be 70 g. This apparent density is known as the *bulk* or *expanded density* (0.7 g/cm^3). If the100 ml cylinder is subsequently tapped, the particles slide past each other and become consolidated. The 70 g of particles that once occupied 100 ml may now only occupy 80 ml. They have an apparent *packed* or *tapped* density (g/cm^3) of 0.875 g/cm^3. Carr's index is a measure of interparticulate forces. If the interparticulate forces are high, powders will have a low bulk density because bridging will occur between particles. This results in a large Carr's index and a large change in volume caused by tapping. If the interparticulate forces are low, particles will have little affinity for one another and will compact spontaneously. Under these circumstances, Carr's index is small and little change in apparent density is induced by tapping. Porosity is the volume ratio occupied by air spaces (voids) between particles of a powder sample.

VII. SOLID HANDLING

A sample of powder is the most complex physical system. No two particles are identical. The properties of the powder are dependent on both the chemical and physical nature of the component and the nature of the interactions between the particles in the powder.

The ability of a powder to pack is dependent on the shape, size, and porosity of the particle.

VIII. MIXING OF POWDERS

Three primary mechanisms are responsible for mixing:

1. Convective movement of relatively large portions of the powder
2. Shear failure, which primarily reduces the scale of segregation
3. Diffusive movement of individual particles

Large-scale mixers
- Rotating shell
- Fixed shell
- Vertical impeller
- Fluid bed

Small-scale mixing
- Mortar and pestle
- Spatula and surface
- Paper bag

Extemporaneous techniques for mixing
- Geometric dilution
- Uniform particle size
- Trituration
- Sieving
- Pulverization by intervention
- Levigation

IX. ORAL POWDERS

Oral powders include headache powders, dusting powders (such as antifungal powders), powders to be reconstituted (such as antibiotics), and insufflations, which are powders intended to be blown into a body cavity such as in the ear or nose. Powder mixtures as a means of measuring small quantities of powders are called triturations.

X. CAPSULES

Capsules are solid dosage forms in which one or more medicinal ingredients and/or inert substances are enclosed within a small shell or container generally prepared from a suitable form of gelatin. Some of the best sources of information about capsules are the companies that manufacture capsule shells. For example, CAPSUGEL® (http://www.capsugel.com/contact.html) provides a lot of very useful information.

What goes into the capsule plays a role in proper capsule selection. Although the industry-leading Coni-Snap (http://www.capsugel.com/products/conisnap.html) capsule is extremely versatile for many formulations, other capsule types are used specifically with liquids or with materials with unique moisture retention properties.

The amount of active ingredient per dose has a direct bearing on the proper size capsule to use. Because capsules usually require less excipients and additives, it is easier to get a more potent dosage without having to use a large-size capsule.

For broad-based appeal, the Coni-Snap® capsule is a proven winner; however, for targeting select consumer

segments, such as vegetarians, Vcaps (http://www.capsugel.com/products/vcaps.html) capsules, which are of plant origin, may better meet customer needs.

Very often, strict governmental regulations are placed on products that are being consumed by the public for health reasons. In most cases, pharmaceutical applications (http://www.capsugel.com/services/rx_dpstdy.html) face different regulatory constraints than do dietary supplements (http://www.capsugel.com/services/ds_dpstdy. html). Capsule shell manufacturers are well acquainted with Regulatory Information and Certification (http://www.capsugel.com/services/regulatory.html) and can alert you to important areas of consideration.

Adding to the complexity to the aforementioned regulatory issue, different countries have varying regulations that need to be considered. For example, regarding the issue of color selection (http://www.capsugel.com/services/color.html), countries have their own specific lists of colorants that can be legally used for capsules.

The appearance of the capsule itself is an important consideration. Colors are known to impact user perception, and the printing of logos on the capsule can increase brand recognition. Because capsules have a long and successful history as the dosage form of choice for pharmaceutical applications (http://www.capsugel.com/services/rx_dpstdy.html) as well as for dietary supplement applications (http://www.capsugel.com/services/dsproduct.html), many options are available for locating capsule-filling-machinery (http://www.capsugel.com/equipment/index.html).

XI. FDA CLASSIFICATION OF CAPSULE TYPES

CAPSULE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin.	CAP	600
CAPSULE, COATED	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; additionally, the capsule is covered in a designated coating.	CAP COATED	602
CAPSULE, COATED, EXTENDED RELEASE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; in addition, the capsule is covered in a designated coating, which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.	CAP COATED ER	611
CAPSULE, COATED PELLETS	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which varying amounts of coating have been applied.	CAP COATED PELLETS	603
CAPSULE, DELAYED RELEASE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, which releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed-release dosage forms.	CAP DR	620
CAPSULE, DELAYED-RELEASE PELLETS	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which enteric coating has been applied, thus delaying release of the drug until its passage into the intestines.	CAP DR PELLETS	621
CAPSULE, EXTENDED RELEASE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, which releases a drug (or drugs) in such a manner to allow a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.	CAP ER	610
CAPSULE, FILM COATED, EXTENDED RELEASE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; in addition, the capsule is covered in a designated film coating, which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.	CAP FILM COATED ER	612
CAPSULE, GELATIN COATED	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin; through a banding process, the capsule is coated with additional layers of gelatin so as to form a complete seal.	CAP GELATIN COATED	605
CAPSULE, LIQUID FILLED	A solid dosage form in which the drug is enclosed within a soluble, gelatin shell that is plasticized by the addition of a polyol, such as sorbitol or glycerin, and is therefore of a somewhat thicker consistency than that of a hard shell capsule; typically, the active ingredients are dissolved or suspended in a liquid vehicle.	CAP LIQ FILLED	606

XII. FDA CLASSIFICATION OF POWDERS

POWDER	An intimate mixture of dry, finely divided drugs or chemicals that may be intended for internal or external use.	PWD	110
POWDER, DENTIFRICE	A powder formulation intended to clean and polish the teeth, and may contain certain additional agents.	PWD DENT	115
POWDER, FOR SOLUTION	An intimate mixture of dry, finely divided drugs or chemicals that, upon the addition of suitable vehicles, yields a solution.	PWD F/SOL	833
POWDER, FOR SUSPENSION	An intimate mixture of dry, finely divided drugs or chemicals that, upon the addition of suitable vehicles, yields a suspension (a liquid preparation containing the solid particles dispersed in the liquid vehicle).	PWD F/SUSP	834
POWDER, METERED	A powder dosage form that is situated inside a container, which has a mechanism to deliver a specified quantity.	PWD MET	841

XIII. INHALERS AND LUNG DELIVERY

Key factors that contribute to the aerodynamic properties of aerosol particles are found in Stokes' law. These factors may be monitored or controlled to optimize drug delivery to the lungs. Predictions of the aerodynamic behavior of therapeutic aerosols can be derived in terms of the physical implications of particle slip, shape, and density. The manner in which each of these properties has been used or studied by pharmaceutical scientists to improve lung delivery of drugs is readily understood in the context of aerosol physics. Additional improvement upon current aerosol delivery of particulates may be predicted by further theoretical scrutiny (*Fundamental Effects of Particle Morphology on Lung Delivery: Predictions of Stokes' Law and the Particular Relevance to Dry Powder Inhaler Formulation and Development.* Timothy M. Crowder, Jacky A. Rosati, Jeffrey D. Schroeter, Anthony J. Hickey, and Ted B. Martonen, *Pharmaceutical Research* 19 (2002) 239–245).

The history of inhaler development in modern times can be traced to the metering valve and propellants (metered dose inhalers, pMDI) used in the treatment of asthma in the 1950s. This was followed closely by somewhat primitive dry powder inhalers (DPIs) in the 1970s. Throughout this period, nebulizers were employed to deliver drugs in aqueous solution. In the past decade, research and development in the field has broadened. This may be explained, in part, by the demise of the Kyoto Treaty on Global Warming (1997), which has refocused activities in the area of alternative propellant formulation. More significantly, there has been an increase in research into alternative approaches to powder and solution formulation and stability. This review is intended to reflect the interest and growth that has occurred in the field of pharmaceutical inhalation aerosol technology in the last 4 years (T.M. Crowder, M.D. Louey, V.V. Sethuraman, H.D.C. Smyth, and A.J. Hickey, 2001: An Odyssey in Inhaler Formulations and Design, *Pharmaceutical Technology* 25(7) (2001) 99–113).

The field of inhalation science is expanding rapidly as scientists are designing delivery systems for proteins and peptides using nanoparticle inhalation systems; the quick absorption through lung surface offers an excellent administration route.

XIV. PROBLEMS IN POWDER HANDLING

Powder materials exhibit a number of technological challenges with their manufacture, storage, transportation, mixing, dusting, characterization, packing, crushing, and milling.

Symptoms of a non-optimized product system utilizing a powder include: unacceptable rehydration, dissolution and solubility rate/reproducibility of the powder mixture; degradation, loss of drug activity, and reduction of product shelf life; drug mixture heterogeneity both before and during use; clogging of spray nozzle; and loss of delivered drug. The following can have a significant impact on the performance of a product using a powder:

- Utilization of the appropriate binders and adhesives
- Disintegrating agents
- Fillers
- Lubricants
- Wetting agents/surfactants
- Glidants
- Flavoring and sweetening agents

Typical powder dispersion problems include:

- Chemical and morphological heterogenity of the surface
- Dissolution or isomorphous substitution of constituent components (metals)
- Dependency of the surface and solution (dissolved or added) ion species

A number of interrelated physicochemical properties, such as pH (acidity), pI (ionic strength), pe (redox), and pc (concentration) influence the properties of the dispersion beside of the pressure and temperature.

XV. CAPSULATION EQUIPMENT

Significant advances have been made within the recent years in automating and validating capsule filling equipment. For example, the German packaging company Bosch Packaging Technology recently introduced a new generation of capsule filling machines. A main feature of the models GKF 701, GKF 1400, and GKF 2500 ASB 100% is the dosing station on the slide-gate principle, which, according to the company, ensures low-loss processing, even for difficult powders. The machine is controlled by an industrial personal computer (PC), using software that complies with the Food and Drug Administration (FDA) 21 CFR part 11 federal regulations. In response to harmful dust that occurs in all areas of pharmaceutical production, Bosch has developed a containment system for its standard blister machine TLT 1400. The system, which produces 400 blisters per minute, protects the operator while processing toxic contents, according to the company. (No endorsement of any manufacturer or product is intended here.) Major suppliers of capsule filling equipment include: Farmatic, Hofliger and Karg, macofar, mGw, and Zanasi.

XVI. CAPSULE FINISHING

Capsules coming off the filling line require dedusting and polishing. These can be done by pan polishing, cloth dusting, and brushing. Commercial equipment to do this includes Rotosort™, Erwek deduser™, and the equipment from Seidenader™. Imprinting on capsules serves many purposes including ready identification. The choice of ink is important.

XVII. MODIFIED-RELEASE PRODUCTS

The capsulation process offers many advantages for designing modified-release products. The simple process of loading the drug onto non-pareil sugar beads and then coating them with a variety of release profiles offers the opportunity of not only separating the incompatible components, but also mixing granules that provide different release profiles, from instant release to step release to prolonged release. Equipment is available to fill several beads simultaneously into capsules, thus assuring dosing accuracies. (If granules with different coatings are mixed, segregation is likely because of the differences in their density.) Coated granules, if compressed, lose their release profiles.

XVIII. CLINICAL TEST SUPPLIES AND PLACEBOS

Encapsulation is the preferred form of drug delivery in preparing placebos and clinical test supplies wherein small runs are planned.

XIX. COATED PARTICLES

Use of hard gelatin capsules allows for the preparation of coated particles to provide modified release or stability; these particles are prepared generally by the method described in Section XVII; however, the possibilities of creating innovative dosage forms using different size of particles makes this dosage form highly desirable for many unstable drugs.

XX. MIXING MECHANISMS

Mixing solids involves a combination of one or more mechanisms of convection, shear, and diffusive mixing. Convection mixing is achieved by the transport of solids such as by blades or screws. Shear mixing results from the forces within the particulate mass; slip planes are set up. This can take place singularly or as a laminar flow. When shear occurs between regions of different composition and parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers. Shear occurring in a direction normal to the interface of such layers is also effective because it reduces segregation. The diffusive mixing is the random motion of particles.

XXI. SEGREGATION MECHANISMS

Particulate solids tend to segregate by virtue of differences in the size, density, shape, and other properties; it can happen during mixing or subsequent storage handling as well. It is important to note that powders that are difficult to flow do not segregate easily because of high interparticulate adhesion; however, because powders must be rendered flowable for the purpose of filling capsules or in bottles or sachet, the segregation phenomenon because very important. Note that often after the addition of magnesium stearate, it is advisable to mix the product only for a limited time because electrical charges on the particles may cause segregation. Often, additives are included in formulations to reduce the tendency of segregation; these components have polarity similar to the components of the formulation. A variety of mixers are designed to counter the segregation during mixing. Regardless of the formulation or equipment used, however, the formulator must conduct a validation study to assure that the product before filling is not segregated and that detailed Manufacturing Directions consequently include such conditions as humidity, mixing speeds, mixing times, and grounding of equipment. It is often said that longer mixing causes

unmixing; this occurs because of segregation as well as abrasion of particles, which alters the particle size distribution profile.

XXII. MIXING EQUIPMENT

Batch mixing is the most common practice using twin-shell, cubic, and cylindrical tumbling mixers on a common shaft. The speed of rotation (generally 30–100 rpm) for these mixers is crucial to good mixing. Other mixers of the same type take the shape of cylinders, cubes, or hexagonal cylinders. The stationary container mixers do not depend on gravity for tumbling as for the preceding mixers; these are useful for mixing sticky, wetted, or plastic mass where shear force is needed to impart mixing. Stationary container mixers include the ribbon blender and the helical flight mixer.

Large mixers produce continuous mixing; large mixers are less consistent in producing uniform mixing and are more useful in the stages where such consistency is not critical.

Selection of equipment depends on the measure of mixing degree required. Manufacturing process validation should include a definition of segregation where large-scale segregation is not present. A large volume of data on the statistics of "degree of mixing" is available where samples are drawn from the mix at various times, and the samples must be of a sufficiently large size to contain enough particles. Perfect mixtures, in statistical terms, are random mixtures. In capsules where pellets of different types are included, these considerations become critical. Let us take the example of a binary mixture where n is the number of particles in the sample and p is the fraction of particles of interest. For example, if a capsule contains 30% of type A pellets, then the average number is 150 in a 500-pellet capsule with standard deviation of:

$$\sigma = \tilde{A}(\text{average})(1 - p)$$

Thus, for the preceding composition, a deviation of 10.2 counts for 150 pellets occurs in each capsule when there is perfect mixing; in this instance, each capsule must be individually sampled because large bulk samples would not reveal the variations.

XXIII. MILLING

Mixing of powders is easier if all components are of the same dimension in particle size. Granulation of powders is done to provide a more uniform particle size; this is a common practice in tablet, capsule, and powder suspension formulations. Milling of granulated mass produces uniform particle size; where dyes are used, milling provides a more uniform mixing and spread of dyes. Lubricants act by coating the particles and require the presence of a certain amount of fines. Size distribution profiles are routinely prepared as part of the development pharmaceutics process, especially where high-speed filling machines are used. Frequency and cumulative plots are made to validate the process. Probability function values found in statistics books should be consulted when designing a robust evaluation program. Particles are measured either microscopically or by weight fractions through a stack of sieves. A sedimentation method is also used for particles in the range of 1–200 μm to obtain a size–weight distribution. Other methods include adsorption, electrical conductivity, light and x-ray scattering, permeametry, and particle trajectory.

During the process of milling or comminution, the particles undergo transformation based on the strain applied, which produces stress, and size reduction begins with the opening of new cracks. If the force applied is not sufficient, then the particle returns to its original state from a stressed state and does not yield. The type of mill used is important, such as a cutter, fluid-energy, hammer, or roller because each provides a special pattern of comminution. For example, is useful for fibrous material, but not for friable material; it produces a product size of 20–80 mesh. The fluid energy mill can produce 1–30 μm particles, and is more suitable for soft and sticky materials. The most common mill is the hammer mill, which is useful for abrasive materials and produces 4–325 mesh particles. In a hammer mill, it matters whether the blades are forward or reversed.